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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IP.Docketing@aporter.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,211	BUERSTEDDE ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,35 and 44-71* is/are pending in the application.

4a) Of the above claim(s) *30,57 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,35,44-56,58-61 and 63-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and submission filed on June 5, 2009 that includes a response to the Office action dated February 9, 2009, has been entered. Claims 29, 35, 55, 56, 60 have been amended and claims 63-71 newly added. No claims were cancelled. Accordingly, claims 29, 30, 35, and 44-62 are pending in the application. Claims 30, 57 and 62 stand withdrawn from further consideration, without traverse, as drawn to non-elected inventions.

The claims have been examined commensurate in scope with the elected invention, and the species of the invention, i.e. chicken, hypermutation, immunoglobulin chain, transcription regulatory element, activity of a target nucleic acid on the cell surface, varying the orientation of the gene conversion donors, and RAD54 protein.

Claims 29, 35, 44-56, 58-61 and 63-71 are under current examination.

Withdrawn Claim Rejections - 35 USC § 102

Claims 29, 35, 44-56, and 58-61 were rejected under 35 U.S.C. 102(e) as being anticipated by Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; filed: Dec. 11, 2003). Applicants have amended base claims 29 and 60 to include the limitation for a lymphoid cell that contains no deleterious mutations in genes encoding XRCC2, XRCC3 or RAD51 analogues, having a hypermutation rate that is higher than the rate of mutation in a lymphoid cell, not taught by Sale et al. Thus the rejection is hereby withdrawn. The claims are however subject to new rejections necessitated by Applicants' amendments, as set forth below. Applicants' arguments are moot in view of the withdrawn rejection.

New Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65, 66, 69 and 70 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 65 and 66 are unclear in their recitation of "hypermutation is at a rate above an order of 10^{-9} to 10^{-10} bp^{-1} $generation^{-1}$". Claims 69 and 70 are unclear in their recitation of "hypermutation…is at least ten times higher".

The claims fail to set an upper limit for the rate of hypermutation, thus failing to define the metes and bounds of the claims.

New Claim Rejections - 35 USC § 112- New Matter

Claim 69 and 70 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims include the limitation "wherein the rate of hypermutation in said genetically modified lymphoid cell is at least ten times higher than the mutation rate in said lymphoid cell". The instant specification is devoid of such description for the newly presented limitations. Applicants state that support for the new claims can be found in the specification as filed, at least, for example, page 8, lines 12-18. However, the referenced paragraph in the specification discloses only the rates that define hypermutation, i.e. those above background, and spontaneous mutation rates observed in PCR. Background mutation rates include those in non-lymphoid cells.

A chicken lymphoid DT cell for example is capable of inducing hypermutation prior to any genetic modification. The cited paragraph is therefore not directed to genetically modified hypermutating lymphoid cells.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of genetically modified lymphoid cells having a hypermutation rate at least ten times higher than their non-genetically modified counterpart, as claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

This is a new matter rejection.

New Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 35, 44-56, 58-61 and 63-71 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 ¶1 "Written Description" Requirement, Rev. 1, 2008; at http://www.uspto.gov/web/menu/written.pdf.

The claims broadly embrace a method for producing a genetically modified lymphoid cell capable of hypermutation at a rate higher than the hypermutation rate in its non-genetically modified counterpart, wherein the cells contain no deleterious mutations in genes encoding RAD51 protein or its analog, necessitating structure/function relationships.

The specification discloses only one lymphoid cell (chicken DT40 $AID^{R}\psi V^{-}$), that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors.

Thus it is clear that Applicants' description of structure and activity regarding other lymphoid cell variants is based in large part on conjecture. The various genetically modified lymphoid cells having a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors and RAD51 were not known in the prior art at the time of the instant invention by Applicants, and include lymphoid cell variants yet to be discovered.

As the specification fails to describe the structure and activity for the genus of variants and genetically modified lymphoid cells, the disclosed single species does not constitute a substantial portion of the claimed genus.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to

> complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

As stated in MPEP 2163 II: If the application as filed does not disclose the complete structure (or acts of a process) of the claimed invention as a whole, determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The instant specification is devoid of a description for the numerous derivatives and variants of lymphoid cell that retain ψV donors and RAD51 gene activity, but have a hypermutation rate higher than that of a non-genetically modified cell. The specification merely discloses the structure and function of DT40 $AID^{R}\psi V^{-}$ lymphoid cell and lymphoid cells having mutations in the RAD51 gene, such as XRCC3, previously described in the prior art, with no other variants or derivatives displaying the requisite biological activity. Thus, Applicants have failed to demonstrate possession of the numerous variants or genetically modified derivatives claimed. Disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate").

The disclosed structural features for the chicken DT $AID^{R}\psi V^{-}$ lymphoid cell, do not constitute an adequate description to demonstrate possession of the numerous possible lymphoid cells that have a hypermutation rate higher than that of a non-genetically modified cell, as claimed. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention

with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11).

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicants have not described the numerous variants and genetically modified lymphoid cell derivatives, that display the requisite biological activities. As such, the Artisan of skill could not predict that Applicant possessed any additional species, except for the chicken DT $AID^{R}\psi V^{-}$ lymphoid cell.

Therefore, the breadth of the claims as reading on numerous variants and genetically modified derivatives of lymphoid cells, that retain the required hypermutation rate, including those yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, and the limited information provided in the specification, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of various variants and genetically modified derivatives of lymphoid cells, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied.

New Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 35, 44-56, 58-61 and 63-71 are newly rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method for selective genetic

diversification of a transgenic target nucleic acid sequence by hypermutation, in a lymphoid cell lacking ψV donors, wherein the lymphoid cell lacking ψV donors is capable of gene conversion prior to deletion of ψV donor sequences, said method comprising introducing a genetic construct comprising said target nucleic acid into the immunoglobulin locus of the lymphoid cell lacking ψV donors, whereby said target nucleic acid sequence is modified by hypermutation; does not reasonably provide an enablement for a method for producing a genetically modified lymphoid cell containing no deleterious mutations in genes encoding RAD51 or its analogs, capable of a hypermutation rate higher than the rate of mutation in a precursor lymphoid cell, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on issues related to the absence of an enabling disclosure for the ability to produce a genetically modified lymphoid cell capable of a hypermutation rate higher than the rate of mutation in a precursor lymphoid cell, that contains no deleterious mutations in the RAD51 gene or its analogs, or any other gene involved in controlling gene conversion and hypermutation. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The claims broadly encompass a method for producing a genetically modified lymphoid cell containing no deleterious mutations in genes encoding RAD51 or its analogs, or any other gene involved in controlling gene conversion and hypermutation, and yet capable of a hypermutation rate higher than the rate of mutation in a precursor lymphoid cell,

As a first issue, it should be noted that the instant base claims 29 and 60 recite method steps that are not commensurate with the preamble of the claimed method. While the method is directed to producing a genetically modified lymphoid cell capable of selective genetic diversification of a transgenic target nucleic acid sequence, the only active method steps in the claims is the transfection of a genetic construct comprising a nucleic acid that is the target of selective genetic diversification by hypermutation. Thus, it is not the step of introducing a target sequence (i.e. the substrate for the hypermutating activity of the cell) that produces a lymphoid cell capable of selective genetic diversification, having a mutation rate higher than the rate of mutation in a precursor lymphoid cell. The claims therefore lack the requisite method steps that can produce a lymphoid cell having increased hypermutation activity.

As a second issue, it should be noted that to produce a genetically modified lymphoid cell (from chicken, rabbit, cows, pigs, excluding humans and mice), capable of increased hypermutation rates, the genes or proteins controlling gene conversion and hypermutation must be selectively modified. Instant claims 29 and 60 only require that the lymphoid cell contain no deleterious mutations in the RAD51 gene or its analogs, and yet be capable of increased rates of hypermutation.

The specification discloses only one lymphoid cell (chicken DT40 $AID^{R}\psi V^{-}$), in the wording examples, that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors, other than the RAD51 gene and its analogs. The skilled artisan would therefore need to engage in further additional experimentation to discover a lymphoid cell having the desired characteristics of higher hypermutation rates with

no deleterious mutations in RAD51 or its analogs. Such experimentation necessarily has unpredictable outcomes and thus constitutes an undue burden on the skilled artisan.

The prior art of Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; of record) teaches a method for generating diversity by preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). The authors teach a cell capable of directed constitutive hypermutation as a genetically manipulated chicken DT40 cell that include mutations in the RAD51, RAD52 and Rad54 genes (Example 8). The prior art appears silent however, on producing lymphoid cells having increased hypermutation rates that are capable of gene conversion as precursors, but carry no mutations in genes controlling gene conversion and hypermutation. Thus, the production of such lymphoid cells is not routine and remains unpredictable.

Therefore, a person of skill in the art would need to engage in further experimentation to determine whether the instantly claimed method would could by carried out in a lymphoid cell that is not deficient in its pseudo V genes. Applicants should also note "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The Federal Circuit has stated that: a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Genentech Inc. v. Novo Nordisk A/S,* 42 USPQ2d 1005 (CAFC 1997).

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation whether the claimed method could be carried out in a lymphoid cell that is not deficient in its pseudo V genes or RAD51 gene and its analogs.

Therefore, in view of the lack of enabling disclosure for the method of producing a lymphoid cell capable of increased hypermutation that has no deficiency in its pseudo V genes or RAD51 gene and its analogs, it would have required undue experimentation for one of skill in the art to perform the method of the claims in achieving said effects. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Conclusion

Claims 29, 35, 44-56, 58-61 and 63-71 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633